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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/816,938 | WANG, BAIYANG | |
| | Examiner | Art Unit | |
| | Michael Szperka | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *29,30,32,33,78,79 and 82-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,32,33,78,79 and 82-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignment*.

## DETAILED ACTION

1. In light of inadvertent typographical errors, the finality of the office action mailed October 26, 2007 has been withdrawn and the action has been vacated. A new office action is set forth below.

2. Applicant's response and amendments received August 6, 2007 are acknowledged.

Claims 1-28, 31, 34-77, 80, and have been canceled.

Claims 29, 33, and 78 have been amended.

Claims 82-125 have been added.

Claims 29, 30, 32, 33, 78, 79, and 82-125 are pending.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claims 29, 30, 32, 33, 78, and 79 under 35 U.S.C. 112, first paragraph, for lack of enablement have been withdrawn in view of applicant's claim amendments received August 6, 2007.

Specifically, these amendments limit the scope of the claims in that they now read only on non-small cell lung cancer, breast cancer, colon cancer and prostate cancer rather than on the genus of all cancer types.

### *Claim Rejections - 35 USC § 102*

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 29, 30, 32, 33, 78, and 79 stand rejected and newly presented claims 82, 88-92, 96, 97, 99, 103-106, 110, 112, 116-119, and 123-125 are rejected under 35 U.S.C. 102(b) as being anticipated by Edgington et al., US Patent 5,223,427 (of record as reference AB1, see entire document) for the reasons of record.

The office action mailed April 6, 2007 states:

> Edgington et al. teach numerous antibodies that bind tissue factor and their methods of use (see entire document, particularly the abstract). Two functionally distinct groups of antibodies that bind tissue factor are disclosed that differ from one another based upon their ability to neutralize tissue factor initiated coagulation (see particularly lines 18-41 of column 21). One particular antibody disclosed by Edgington et al. that does not inhibit tissue factor mediated blood coagulation is TF9-10H10 (see particularly lines 35-41 of column 21). Antibodies that do not inhibit tissue factor mediated coagulation are taught as being used in methods of treating breast and lung cancer when the antibodies are coupled to anti-tumor agents and administered as part of an anti-tumor therapeutic composition (see particularly lines 3-11 of column 23). Anti-tumor agents are disclosed as comprising radionuclides such as $^{131}$I (see particularly lines 12-17 of column 23). Note that $^{131}$I is a "cytotoxic agent" as per paragraph 102 of the instant specification and that breast and lung carcinomas are "solid tumors" as per paragraph 151 of the instant specification. The non-tissue factor inhibiting antibody TF9-10H10 is also disclosed for use in in vivo and in vitro methods of detecting expression of human tissue factor (see particularly from line 67 of column 3 to line 26 of column 4, lines 1-53 of column 26. The antibodies used in such methods can be detected through either secondary reagents or by directly coupling a detectable reagent to said antibodies (see particularly lines 20-64 of column 24). Note that TF9-10H10 is a whole murine antibody molecule and therefore it comprises an Fc domain that can participate in Fc-mediated mechanisms.
>
> Therefore, the prior art anticipates the claimed invention.

Applicant's arguments filed August 6, 2007 have been fully considered but they are not persuasive. Applicant argues that Edgington et al. do not disclose the dosage range recited in the independent claims as currently amended.

This argument is not persuasive because in the paragraph spanning columns 22 and 23 Edgington et al. disclose antibody dosages that fall within the recited dosage range, and thus the dosages of anti-tissue factor antibodies disclosed by Edgington et al. anticipate the instant recited range.

Applicant also argues that Edgington et al. do not disclose that their antibodies "cause an increase in percent cytotoxicity of tissue factor positive cells as compared to a negative control antibody."

This argument is not persuasive because the monoclonal antibodies of Edgington et al. are disclosed as full length murine antibodies and as such are competent to partake in Fc mediated cytotoxicity reactions including complement-

dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). Specifically, antibody TF9-10H10 is disclosed as being a murine IgG1 antibody (see Table 8). It is well know in the art that murine IgG1 mediates ADCC (Greenberg et al., see entire document, particularly the title, abstract, and Table II). The antibodies of Edgington et al. are further disclosed as being conjugated to cytotoxic agents, such as the radioisotope $^{131}$I. As such, the antibodies of Edgington et al. inherently comprise cytotoxicity, both intrinsically due to their isotype and via conjugation to cytotoxic agents. Further, it appears that cytotoxicity is the scientific mechanism explaining why the antibodies of Edgington et al. comprise the ability to be used in methods of treating cancer. Applicant is reminded that "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

It is noted that in response to the previous office action, applicant has added many new claims reciting dependent limitations not addressed in the rejection of record. One such limitation is that the administered product is the "product of a Fab expression library". Applicant is reminded that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Note that the dependent claims recite a method of using a product made by a certain process. As such, the administered antibody in the dependent methods must be an antibody Fab fragment, but the Fab fragment can be

made by any process. Edgington et al. disclose that Fab are to be administered to patients in the paragraph spanning columns 22 and 23 and thus Edgington et al. disclose the recited limitation.

Applicant has also added dependent claims such that the administered antibodies either "bind the same epitope as" or "compete for binding with" specifically named monoclonal antibodies. Given that the antibodies of Edgington et al. comprise the properties of binding human tissue factor, not inhibiting tissue factor mediated coagulation, comprise cytotoxicity, are administered in dosages which anticipate the instant recited dosages, and are disclosed as being administered to treat diseases recited in the instant claims, the antibodies of Edgington et al. bind the same epitopes as and thus compete for binding with named antibodies TF260, TF278, and TF392 because the function consequences of administration of the antibodies of Edgington et al. and the named antibodies are the same, i.e. the successful treatment of cancer, including breast cancer.

### *Claim Rejections - 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 29, 30, 32, 33, 78, and 79 stand rejected and newly presented claims 82, 88-92, 96, 97, 99, 103-106, 110, 112, 116-119, and 123-125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1 on the 11/9/04 IDS, see entire document) in view of Koomagi et al. (of record as reference AS5 on the 11/9/04 IDS, see entire document) for the reasons of record.

The office action mailed April 6, 2007 states:

> The teachings of Edgington et al. have been discussed supra. These teachings differ from the instant claimed invention in that while they teach the detection and treatment of lung carcinomas, they do not specifically teach non-small-cell lung carcinomas.

Koomagi et al. teach that they observed a significant association between the expression of tissue factor on tumor cells and the susceptibility of the tumor cells to chemotherapy (see entire document, particularly the abstract). They further teach that tissue factor expression has predictive value in estimating survival for patients with non-small-cell lung cancer (see particularly the last sentence of the abstract and the penultimate paragraph of page 21). Specifically, they observed tumors that express tissue factor were generally more susceptible to treatment with an anti-tumor agent, and that patients who had tissue factor positive tumors tended to have shorter survival times (see particularly the abstract, Figure 2, and Table IV).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the methods of Edgington et al. that comprise the use of non-inhibitory antibodies that bind tissue factor in order to treat non-small-cell lung cancer. Motivation to do so comes from the teachings of Koomagi et al. that detection of tissue factor expression is of prognostic value in non-small-cell lung cancer and the teachings of Edgington et al. which set forth multiple ways by which tissue factor expression can be detected using non-inhibitory antibodies that bind tissue factor. A person of ordinary skill in the art would have been further motivated to treat patients with non-small-cell lung cancer using the treatment methods of Edgington et al. because Edgington et al. disclose that their treatment method is to be used to treat all lung carcinomas, a genus that comprises non-small-cell carcinoma, and because Koomagi et al. teach that tissue factor expressing tumors are more amenable to treatment with anti-tumor agents. As such, an anti-tissue factor antibody conjugated to a cytotoxic agent, such as those disclosed by Edgington et al., would be reasonably expected to bind tissue factor expressing non-small-cell lung cancer cells and kill said cells since such cells comprise an increased susceptibility to therapeutic agents as taught by Koomagi et al.

Applicant's arguments filed August 6, 2007 have been fully considered but they are not persuasive. Applicant argues that the references, either alone or in combination, do not disclose the limitations of the recited dosage range and "inherent" cytotoxicity of the anti-tissue factor antibody.

This argument is not persuasive for the reasons discussed in the rejection set forth under 35 USC 102 above and will not be addressed further.

9. The following are new grounds of rejection necessitated by applicant's claim amendments received August 6, 2007.

10. Claims 91-93, 105-107, and 118-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims recite methods utilizing antibodies "obtained from a hybridoma cell line TF260 deposited under ATCC Accession No. PTA-5197, a hybridoma cell line TF278 deposited under ATCC Accession No. PTA-5676, or a hybridoma cell line TF392 deposited under ATCC Accession No. PTA-5677" and as such these antibodies are a required element needed to make and use the claimed invention. As a required element, these antibodies must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell line. See 37 CFR 1.801-1.809.

The instant specification does not appear to disclose that cell lines secreting the recited antibodies have been deposited under the Budapest Treaty or provide assurances that the recited material will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, and that said material will be replaced if the material becomes unviable.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that PTA-5197, PTA-5676, and PTA-5677 have been deposited under the Budapest Treaty and that PTA-5197, PTA-5676, and PTA-5677 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent, whichever is longer. See 37 CFR 1.806 and MPEP 2410-2410.01. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR

1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the vector described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

11. Claims 29, 30, 32, 33, 78, 79, 82-92, 94-106, 108-119, and 121-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant has amended independent claims 29, 33 and 78 to recite the limitation that the genus of antibodies that are used in the claimed methods comprise the functional property of causing "an increase in percent cytotoxicity of tissue factor positive cells compared to a negative control antibody". Applicant has argued that support for such a limitation can be found in paragraph 205 on page 79, in Figures 4A-4C, and in the originally filed claims.

This argument is not persuasive because the paragraph and Figures cited for support pertain to disclosed working examples comprising antibodies TF260, TF278, and TF392. As such, this disclosure of increasing cytotoxicity is only pertinent to the specifically named antibodies and is not disclosed as applying to the entire genus of recited anti-tissue factor antibodies. Further, the original claims (see particularly claims 2, 3, and 6) disclose cytotoxicity mediated by complement (CDC), mediated by antibody-dependent cell-mediated cytotoxicity (ADCC), and mediated by conjugation to a cytotoxic moiety, yet the breadth of the instant claims is not limited to these three

mechanisms. Applicant has not pointed other locations in the specification where the limitation of cytotoxicity by any and all mechanisms is disclosed generically as pertaining to the recited genus of anti-tissue factor antibodies. Therefore, it appears that applicant's amendments received August 6, 2007 have introduced new matter into the claimed invention.

12. Claims 91, 92, 94, 95, 105, 106, 108, 109, 118, 119, 121, and 122 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed broad methods comprising the administration of an anti-tissue factor antibody wherein the anti-tissue factor antibody comprises one member of the genus of SEQ ID NOs:6, 8, 19, 21, and 27, or comprises a sequence encoded by the genus of SEQ ID NOs:5, 7, 18, 20, and 26. The specification discloses that SEQ ID NO:6 is the VH domain of TF260, SEQ ID NO:8 is the VL domain of TF260, SEQ ID NO:19 is the VH domain of TF278, SEQ ID NO:21 is the VL domain of TF278, and SEQ ID NO:27 is the VH domain of TF392. Note that the recited polynucleotides encode the recited polypeptide sequences, for example SEQ ID NO:5 encodes SEQ ID NO:6. The specification indicates that antibodies TF260, TF278, and TF392 comprise the recited functional properties. The breadth of the claims is such that only half of the structure of the antibody to be used in the claimed methods is positively recited.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

The specification discloses intact antibodies which comprise VH and VL domains which were obtained by standard hybridoma technology following immunization of mice with human tissue factor. It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the

contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., Immunobiology, third edition, 1997, pages 3:7-3:11, see entire selection). As such, the art indicates that more structural information is required to ensure antigen binding than what is to be found in an isolated antibody variable domain. Indeed, Steipe et al. disclose an antibody which comprises a sequence 100% identical to SEQ ID NO:8 of the instant specification, yet this antibody is not disclosed as binding tissue factor (US Patent 6,262,238, see entire document and the attached sequence alignment). The specification does not disclose that the recited sequences by themselves comprise the recited properties including tissue factor binding. Further, the specification does not appear to disclose sequences with which the recited sequences can be combined (excepting the combinations of SEQ ID NOs:6/8, 19/21, and 27/29 which reconstitute the variable domains of antibodies TF260, TF278, and TF392 respectively) to yield antibodies that comprise the recited properties. As such as skilled artisan would reasonably conclude that applicant was not in possession of the claimed genus of antibodies that comprise the recited functional properties and comprise only one of the recited SEQ ID numbers.

Applicant has also claimed antibodies that bind to either the same epitope as or compete for binding with antibodies TF260, TF278, and TF392. The specification does not appear to disclose what domain/region/structure within human tissue factor these antibodies bind, and it is not clear if these antibodies bind the same epitope or bind distinct epitopes. As discussed above, the antibodies were made by immunizing mice with full length human tissue factor, and so the method by which the antibodies were made does not aid in determining the structure that is bound by the recited antibodies. Therefore, the specification does not appear to comprise an adequate written description of the epitope bound by antibodies which bind the same or competing epitopes of TF260, TF278, and TF392 since the epitopes bound by antibodies TF260, TF278, and TF392 are not disclosed. As such, a skilled artisan would reasonably

conclude that applicant was only in possession of TF260, TF278, and TF392 and was not in possession of antibodies that bound the same or competing epitopes as said antibodies at the time the instant invention was filed.

13. Claims 85, 87, 100, 102, 113, and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1, see entire document) in view of Kipriyanov et al. (Molecular Biotechnology, 1999, 12:173-201).

The teachings of Edgington et al. have been discussed above. These teachings differ from the instant claimed invention in that Edgington et al. do not disclose that the antibodies used in their methods are chimeric or humanized antibodies.

Kipriyanov et al. disclose that it is routine in the art to make chimeric and humanized antibodies based upon a starting murine antibody for therapeutic use because when murine antibodies are administered to humans, the human immune system recognizes the administered antibody as foreign and mounts an immune response directed to the administered antibody. This unwanted immune response reduces the efficacy of the administered antibody and is known as the HAMA response. By altering the structure of the administered antibody to make it more similar in structure to a human antibody, via either chimeric or humanized antibody technology, the resulting antibody is more suitable for human administration because it is less likely to elicit the unwanted HAMA response (see entire document, particularly sections 1-3).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the antibodies of Edgington et al. into chimeric or humanized forms for use in methods disclosed by Edgington et al. Motivation to do so comes from the fact that Edgington et al. disclosed methods of administration to human patients and Kipriyanov et al. disclose that chimeric or humanized antibodies are preferred as compared to murine antibodies for administration to humans because chimeric and humanized antibodies have reduced immunogenicity and thus are less likely to elicit a neutralizing HAMA response.

14. Claims 85, 87, 100, 102, 113, and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1 on the 11/9/04 IDS) in view of Koomagi et al. (of record as reference AS5 on the 11/9/04 IDS) as applied to claims 29, 30, 32, 33, 78, 79, 82, 88-92, 96, 97, 99, 103-106, 110, 112, 116-119, and 123-125 above, and further in view of Kipriyanov et al. (Molecular Biotechnology, 1999, 12:173-201).

The teachings of Edgington et al. and Koomagi et al. have been discussed above. These teachings differ from the instant claimed invention in that they do not disclose that the antibodies used in their methods are chimeric or humanized antibodies.

Kipriyanov et al. disclose that it is routine in the art to make chimeric and humanized antibodies based upon a starting murine antibody for therapeutic use because when murine antibodies are administered to humans, the human immune system recognizes the administered antibody as foreign and mounts an immune response directed to the administered antibody. This unwanted immune response reduces the efficacy of the administered antibody and is known as the HAMA response. By altering the structure of the administered antibody to make it more similar in structure to a human antibody, via either chimeric or humanized antibody technology, the resulting antibody is more suitable for human administration because it is less likely to elicit the unwanted HAMA response (see entire document, particularly sections 1-3).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the antibodies of Edgington et al. into chimeric or humanized forms for use in methods of human administration rendered obvious by the disclosure of Edgington et al. in view of Koomagi et al. Motivation to do so comes from Kipriyanov et al. who disclose that chimeric or humanized antibodies are preferred as compared to murine antibodies for administration to humans because chimeric and humanized antibodies have reduced immunogenicity and thus are less likely to elicit a neutralizing HAMA response.

15. Claims 83, 98, and 111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1, see entire document) in view of Caron et al. (J Exp Med, 1992, 176:1191-1195).

The teachings of Edgington et al. have been discussed above. These teachings differ from the instant claimed invention in that Edgington et al. do not disclose that the antibodies used in their methods are "modified" antibodies. The specification discloses in paragraph 45 of page 12 that "modified" antibodies comprise either mutations in the Fc region that increase effectors function or comprise specific glycosylation patters that confer enhanced ADCC activity.

Caron et al. disclose that mutating a serine to cysteine in the Fc of an IgG1 antibody allows for the formation of interchange disulfide bonds. Antibodies altered in this manner demonstrated increased ability to be internalized and retain radioisotopes in tumor target cells as well as increased complement mediated (CDC) and antibody-dependent cellular cytotoxicity (ADCC) and thus are more advantageous than naturally occurring antibodies for the treatment of cancers (see entire document, particularly the abstract).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to modify the antibodies disclosed by Edgington et al. for use in methods of in vivo administration to comprise a mutated Fc region that allows for interchange homodimerization. Motivation to do so comes from the disclosure of Edgington et al. that their antibodies are to be used in identifying and treating cancer and the disclosure of Caron et al. that antibodies modified by their teachings are more effective at targeting and killing cancerous tumor cells due to increased internalization, CDC and ADCC activities.

16. Claims 83, 98, and 111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1 on the 11/9/04 IDS) in view of Koomagi et al. (of record as reference AS5 on the

11/9/04 IDS) as applied to claims 29, 30, 32, 33, 78, 79, 82, 88-92, 96, 97, 99, 103-106, 110, 112, 116-119, and 123-125 above, and further in view of Caron et al. (J Exp Med, 1992, 176:1191-1195).

The teachings of Edgington et al. in view of Koomagi et al. have been discussed above. These teachings differ from the instant claimed invention in that they do not disclose that the antibodies used in their methods are "modified" antibodies. The specification discloses in paragraph 45 of page 12 that "modified" antibodies comprise either mutations in the Fc region that increase effector function or comprise specific glycosylation patters that confer enhanced ADCC activity.

Caron et al. disclose that mutating a serine to cysteine in the Fc of an IgG1 antibody allows for the formation of interchain disulfide bonds. Antibodies altered in this manner demonstrated increased ability to be internalized and retain radioisotopes in tumor target cells as well as increased complement mediated (CDC) and antibody-dependent cellular cytotoxicity (ADCC) and thus are more advantageous than naturally occurring antibodies for the treatment of cancers (see entire document, particularly the abstract).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to modify the antibodies disclosed by Edgington et al. for use in methods of in vivo administration rendered obvious by the disclosure of Edgington et al. in view of Koomagi et al. to comprise a mutated Fc region that allows for interchain homodimerization. Motivation to do so comes from the methods of identifying and treating cancer rendered obvious by the disclosures of Edgington et al. and Koomagi et al. and the disclosure of Caron et al. that antibodies modified by their teachings are more effective at targeting and killing cancerous tumor cells due to increased internalization, CDC and ADCC activities.

17. Claims 86, 101, and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1,

see entire document) in view of Huston et al. (US Patent 5,534,254, see entire document).

The teachings of Edgington et al. have been discussed above. These teachings differ from the instant claimed invention in that Edgington et al. do not disclose that the antibodies used in their methods are single chain antibodies.

Huston et al. teach methods of making and using single chain antibodies (see entire document, particularly the abstract). Single chain antibodies offer the advantage of superior in vivo pharmokinetic properties due to the accelerated rates of tissue biodistribution, enhanced target specificity, and fast clearance rates of single chain antibodies as compared to whole antibody molecules (see particularly lines 45 to 55 of column 9).

Therefore, it would have been obvious to a person of ordinary skill in the art to make the antibodies disclosed by Edgington et al. into single chain antibodies as taught by Huston et al. for use in the treatment methods of Edgington et al. Motivation to do so comes from the teachings of Edgington that their antibodies are to be used for in vivo methods of administration and the teachings of Huston et al. that single chain antibodies are more advantageous for in vivo administration methods due to the advantages of accelerated rates of biodistribution, enhanced target specificity and fast clearance rates that single chain antibodies provide in comparison to whole antibody.

18. Claims 86, 101, and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al., US Patent 5,223,427 (of record as reference AB1 on the 11/9/04 IDS) in view of Koomagi et al. (of record as reference AS5 on the 11/9/04 IDS) as applied to claims 29, 30, 32, 33, 78, 79, 82, 88-92, 96, 97, 99, 103-106, 110, 112, 116-119, and 123-125 above, and further in view of Huston et al. (US Patent 5,534,254, see entire document).

The teachings of Edgington et al. and Koomagi et al. have been discussed above. These teachings differ from the instant claimed invention in that they do not disclose that the antibodies used in their methods are single chain antibodies.

Huston et al. teach methods of making and using single chain antibodies (see entire document, particularly the abstract). Single chain antibodies offer the advantage of superior in vivo pharmokinetic properties due to the accelerated rates of tissue biodistribution, enhanced target specificity, and fast clearance rates of single chain antibodies as compared to whole antibody molecules (see particularly lines 45 to 55 of column 9).

Therefore, it would have been obvious to a person of ordinary skill in the art to make the antibodies disclosed by Edgington et al. into single chain antibodies as taught by Huston et al. for use in the administration methods rendered obvious by the disclosure of Edgington et al. in view of Koomagi et al. Motivation to do so comes from the disclosure of Huston et al. that single chain antibodies are more advantageous for in vivo administration methods due to the advantages of accelerated rates of biodistribution, enhanced target specificity and fast clearance rates that single chain antibodies provide in comparison to whole antibody.

19. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 88, 103, and 116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Dependent claims 88, 103, and 116 recite the administration of antibodies which are the products of Fab expression libraries. As such, the most reasonable interpretation of the claims is that the method requires the administration of a Fab fragment. However, these claims depend from independent claims 29, 33, and 78 which recite antibodies that "cause an increase in percent cytotoxicity of tissue factor positive cells compared to a negative control antibody." Applicant has argued as part of the response received August 6, 2007 that the antibodies of the independent claim comprise intrinsic cytotoxicity (i.e. they are not cytotoxic because they are conjugated to

a cytotoxic agent), and it is known in the art that the Fc domain of an antibody confer effector function, such as cytotoxicity. Applicant's interpretation of claim scope is supported by the recitation of antibodies conjugated to cytotoxic moieties in other dependent claims. Note that a Fab does not comprise an Fc domain, and that dependent claims 88, 103, and 116 do not depend from claims reciting conjugation to cytotoxic moieties. As such, it is unclear how the antibodies administered in claims 88, 103, and 116 comprise cytotoxic activity. It is also appears that dependent claims 88, 103, and 116 do not further limit the claimed invention because the structure of the administered agent removes the functional limitation of cytotoxicity recited in the independent claims. Altering claim dependency is one way to clarify the issues raised in this rejection.

21. No claims are allowable.

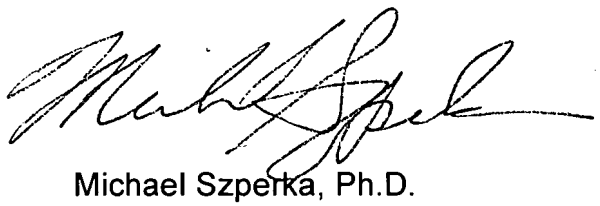
22. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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Art Unit 1644
December 6, 2007